under 35 U.S.C. § 101. Claims 1-17 and 19-50 have been rejected under 35 U.S.C. § 112, first paragraph. Claim 18 has been rejected under 35 U.S.C. § 101 and § 112, first paragraph. Claims 36-50 have been rejected under 35 U.S.C. § 112, first paragraph. Claims 1-50 have been rejected under 35 U.S.C. § 112, second paragraph.. Claims 1-15, 18-33 and 35 have been rejected under 25 U.S.C. § 112, second paragraph. For the reasons set forth herein, each of the Examiner's rejections is overcome.

2. ***Amendments***

Claims 1, 5, 19, 23, 36 and 43 have been amended. More particularly, in accordance with the Examiner's suggestion, independent claims 1, 19 and 36 have been amended to delete "general" from the phrase "an aspartyl protease inhibitor having the general formula. . . ." In addition, dependent claims 5, 23 and 43 have been amended to correct the minor error noted by the Examiner. Such amendments relate to formal matters and, thus, no new matter has been introduced. Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

3. ***The Abstract***

In the Office Action, the abstract was objected to as allegedly being too short and generic (*see*, page 2 of the Office Action). The Examiner indicated that this objection could be overcome by amending the abstract to include, for example, claim 1.

In order to expedite prosecution, the abstract has been amended to include the subject matter recited in claim 1. In view of the amendment to the abstract, the Examiner's concern is overcome. Accordingly, Applicants urge the Examiner to withdraw this objection.

4. ***The Priority Claim***

In the Office Action, the Examiner indicated that "[a]n application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR § 1.78)" (*see*, page 2 of the Office Action).

Applicants respectfully point out that when the above-referenced patent application was originally filed, the transmittal sheet requested that page 1 of the specification been to specifically refer to the earlier filed patent applications. More particularly, the transmittal sheet stated:

> Please amend this application by adding the following before the first sentence: "This application is a continuation-in-part of 09/018,226 and claims the benefit of that application, U.S. Provisional Application No. 60/125,958, filed March 24, 1999, and U.S. Provisional Application No. 60/036,903, filed February 4, 1997, the disclosures of which are incorporated by reference."

As such, the above-referenced patent application does, in fact, contain a specific reference to the prior applications in the first sentence of the specification. Accordingly, Applicants urge the Examiner to withdraw this objection.

5. Rejections Under 35 U.S.C. § 101

Claims 1-50 have been rejected under 35 U.S.C. § 101 as allegedly lacking utility. Each of the Examiner's concerns and, in turn, Applicants' responses to those concerns are set forth hereinbelow.

a. The Examiner has rejected claims 1-16 and 18-50, stating that the claimed invention is not supported by either a credible asserted utility or a well-established utility. For the reasons set forth herein, Applicants respectfully traverse this rejection.

Independent claim 1 and dependent claims 2-18 are directed to a method for modulating the processing of an amyloid precursor protein (APP), the method comprising contacting a composition containing the APP with as aspartyl protease inhibitor of Formula I. As explained in the specification, the modulation of APP can be demonstrated in a variety of ways (*see, e.g.*, page 31, lines 7-22, of the specification). For instance, aspartyl protease inhibitors can be evaluated for their ability to modulate generation of Aβ or α-sAPP. In one preferred embodiment, the formation of Aβ is decreased compared to the amount formed in the absence of the aspartyl protease inhibitor. In another preferred embodiment, formation of α-sAPP is increased compared to the amount formed in the absence of the aspartyl protease inhibitor. The specification and, in particular, the examples provided therein disclose that the aspartyl protease inhibitors of Formula I can, in fact, be used to modulate the processing of an APP.

As such, since claims 1-18 are directed to a specific method of use and the specification clearly provides evidence that points to an activity for the aspartyl protease inhibitors of Formula I that is consistent with that method of use, the claimed invention has a specific, substantial and credible utility.

In addition, independent claim 19 and dependent claims 20-35 are directed to a method for modulating the processing of a tau-protein (τ-protein), the method comprising contacting a composition containing the τ-protein with an aspartyl protease inhibitor of Formula

I. As explained in the specification, the modulation of a tau-protein can be demonstrated in a variety of ways (*see, e.g.*, page 34, lines 5-18, of the specification). For instance, aspartyl protease inhibitors can be evaluated for their ability to modulate generation of tau-fragments. In one preferred embodiment, the formation of tau-fragments is decreased compared to the amount formed in the absence of the aspartyl protease inhibitor. The specification and, in particular, the examples provided therein disclose that the aspartyl protease inhibitors of Formula I can, in fact, be used to modulate the processing of a τ-protein.

As such, since claims 19-35 are directed to a specific method of use and the specification clearly provides evidence that points to an activity for the aspartyl protease inhibitors of Formula I that is consistent with that method of use, the claimed invention has a specific, substantial and credible utility.

Moreover, independent claim 36 and dependent claims 37-50 are directed to a method for treating a neurodegenerative disorder, the method comprising: administering to a mammal a therapeutically effective amount of an aspartyl protease inhibitor of Formula I. As explained in the specification, neurodegenerative disorders that can be treated using the aspartyl protease inhibitors of the present invention include, for example, those neurodegenerative disorders characterized by the accumulation of amyloid plaques or τ-protein. Examples of such neurodegenerative diseases include, but are not limited to, the following: Alzheimer's disease, Parkinson's disease, cognition deficits, Downs Syndrome, cerebral hemorrhage with amyloidosis, dementia (e.g., dementia pugilistica) and head trauma. Again, as explained above, the specification and, in particular, the examples provided therein disclose that the aspartyl protease inhibitors of Formula I can, in fact, be used to modulate the processing of an APP and a τ-protein.

As such, since claims 36-50 are directed to a specific method of use and the specification clearly provides evidence that points to an activity for the aspartyl protease inhibitors of Formula I that is consistent with that method of use, the claimed invention has a specific, substantial and credible utility.

b. The Examiner has rejected claim 18, stating that this claim is directed to increasing amyloid production and the specification fails to make clear the benefit of this.

Applicants have reviewed claim 18 and it is thought that the Examiner intended to reject claim 16 and not claim 18. Claim 16 is directed to the method of claim 1, whereby formation of amyloidogenic Aβ peptides (Aβ) is decreased compared to the amount formed in the absence of the aspartyl protease inhibitor. As explained in the specification, this is one way in

which the modulation of APP can be demonstrated. Moreover, as explained in the specification, amyloidogenic Aβ peptides are the principal component of the amyloid plaques. As such, clearly there is a benefit to being able to decease the formation of amyloidogenic Aβ peptides.

As such, since claim 16 is directed to a specific method of use and the specification clearly provides evidence that points to an activity for the aspartyl protease inhibitors of Formula I that is consistent with that method of use, claim 16 has a specific, substantial and credible utility.

6. Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1-50 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly non-enabled. Each of the Examiner's concerns and, in turn, Applicants' responses to those concerns are set forth hereinbelow.

a. The Examiner has rejected claims 1-17 and 19-50, stating that the claimed invention is not supported by either a credible asserted utility or a well established utility for the reasons set forth above in connection with the § 101 rejection.

As explained above, the invention recited in claims 1-50 has a specific, substantial and credible utility. As such, the rejection under 35 U.S.C. § 112, first paragraph, is improper and should be withdrawn.

b. The Examiner has rejected claim 18, stating that the claimed invention is not supported by either a credible asserted utility or a well established utility for the reasons set forth above in connection with the § 101 rejection.

As explained above, it is Applicants understanding that the Examiner intended to reject claim 16, not claim 18. Moreover, as explained above, the invention recited in claim 16 does, in fact, have a specific, substantial and credible utility. As such, the rejection under 35 U.S.C. § 112, first paragraph, is improper and should be withdrawn.

c. The Examiner has rejected claims 36-50, as allegedly nonenabled. In making this rejection, the Examiner has alleged that the scope of the phrase "neurodegenerative disorders" cannot be deemed enabled. Applicants respectfully traverse this rejection.

As explained above, independent claim 36 and dependent claims 37-50 are directed to a method for treating a neurodegenerative disorder, the method comprising: administering to a mammal a therapeutically effective amount of an aspartyl protease inhibitor of Formula I. As explained in the specification, neurodegenerative disorders that can be treated using the aspartyl protease inhibitors of the present invention include, for example, those neurodegenerative disorders characterized by the accumulation of amyloid plaques or τ-protein.

Examples of such neurodegenerative diseases include, but are not limited to, the following: Alzheimer's disease, Parkinson's disease, cognition deficits, Downs Syndrome, cerebral hemorrhage with amyloidosis, dementia (e.g., dementia pugilistica) and head trauma. Again, as explained above, the specification and, in particular, the examples provided therein disclose that the aspartyl protease inhibitors of Formula I can, in fact, be used to modulate the processing of an APP and a τ-protein.

In view of the foregoing remarks, Applicants respectfully submit that the phrase "neurodegenerative disorder," when read in view of the specification, is fully enabled by the specification as originally filed. Accordingly, Applicants urge the Examiner to withdraw the rejection under 35 U.S.C. § 112, first paragraph.

7. ***Rejections Under 35 U.S.C. § 112, Second Paragraph***

Claims 1-50 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Each of the Examiner's concerns and, in turn, Applicants' responses to those concerns are set forth hereinbelow.

a. The Examiner has rejected claims 1-50, stating that the use of the word "general" in claims 1, 19 and 36 renders them indefinite.

Applicants respectfully submit that the phrase "general formula" is used in claims 1, 19 and 36 to indicate that a genus of compounds, which have a common core structure, is being claimed. It is noted that the phrase "general formula" is typically used in patent claims and its use does not imply to those of skill in the art that other formulae are being claimed. However, in order to expedite prosecution, Applicants have amended claims 1, 19 and 36 to delete the word "general." Accordingly, Applicants urge the Examiner to withdraw this rejection.

b. The Examiner has rejected claims 5, 23 and 43, stating that the last two formulae in each of these claims contains a double bond and not a single bond.

In order to expedite prosecution, claims 5, 23 and 43 have been amended to correct the last two formulae so that they properly show a single bond and not a double bond. In view of this amendment to claims 5, 23 and 43, the Examiner's concern is overcome. Accordingly, Applicants urge the Examiner to withdraw this rejection.

c. The Examiner has objected to the claims, stating that (1) the definitions in the specification use open language (*i.e.*, "such as"); and (2) the definition of heteroaryl is unclear.

Applicants respectfully point out that the phrase "such as" in the definition section is used to refer to "examples" of a defined substituent or functional group. Such examples are

intended to be illustrative and not intended to limit the scope of the substituent or functional group being defined. For instance, the phrase "substituted alkyl" is defined as an alkyl group including one or more functional groups (*see*, page 11 of the specification). The specification then goes on to list examples of functional groups with which the alkyl group can be substituted. Again, the examples of functional groups provided in the specification are intended to be illustrative and are not intended to limit the scope of the functional group to those specifically recited.

In addition, Applicants respectfully point out that the specification provides a definition for "heteroaryl" on page 13, lines 13-22, of the specification. As defined therein, "heteroaryl" refers to aromatic ring(s) in which one or more carbon atoms of the aromatic ring(s) are substituted by a heteroatom such as nitrogen, oxygen or sulfur. As such, the term "heteroaryl" is, in fact, defined in the specification, and it is defined in a manner that it is consistent with the term "heterocycle."

In view of the foregoing, Applicants respectfully submit that the use of "such as" in connection with the definitions of the various substituents set forth in the claims does not render the claims indefinite. Moreover, the use of the term "heteroaryl" in the claims does not render the claims indefinite. Accordingly, Applicants urge the Examiner to withdraw this rejection under 35 U.S.C. § 112, second paragraph.

d. The Examiner has rejected claims 1 and 19, stating that the use of the term "modulate" in claims 1 and 19 is unclear.

Applicants respectfully point out that the use of the term "modulate" is not unclear when read in view of the specification. For instance, claim 1 is directed to "a method for modulating the processing of an amyloid precursor protein (APP)." As explained in the specification, the modulation of APP can be demonstrated in a variety of ways (*see*, *e.g.*, page 31, lines 7-22, of the specification). For instance, aspartyl protease inhibitors can be evaluated for their ability to modulate generation of Aβ or α-sAPP. In one preferred embodiment, the formation of Aβ is decreased compared to the amount formed in the absence of the aspartyl protease inhibitor. In another preferred embodiment, formation of α-sAPP is increased compared to the amount formed in the absence of the aspartyl protease inhibitor. The specification provides numerous *in vitro* and *in vivo* assays that can be used to screen a given aspartyl protease inhibitor for its ability to modulate APP processing.

Similarly, claim 19 is directed to "a method for modulating the processing of a tau-protein." As explained in the specification, the modulation of a tau-protein can be

demonstrated in a variety of ways (*see, e.g.*, page 34, lines 5-18, of the specification). For instance, aspartyl protease inhibitors can be evaluated for their ability to modulate generation of tau-fragments. In one preferred embodiment, the formation of tau-fragments is decreased compared to the amount formed in the absence of the aspartyl protease inhibitor. Again, the specification provides numerous *in vitro* and *in vivo* assays that can be used to screen a given aspartyl protease inhibitor for its ability to modulate the processing of a tau-protein.

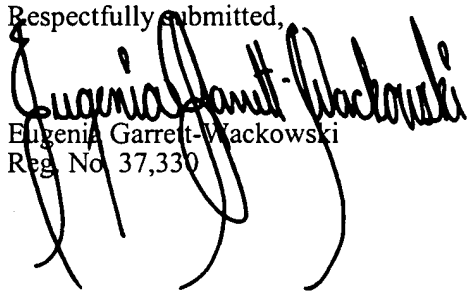
In view of the foregoing, Applicants respectfully submit that the use of the term "modulating" in claims 1 and 19 does not render the claims indefinite. Accordingly, Applicants urge the Examiner to withdraw this rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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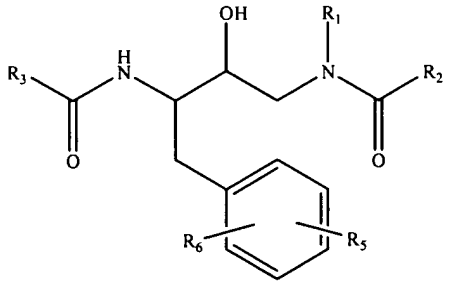
VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the abstract

The Abstract has been amended as follows:

The present invention relates to (i) non-peptide aspartyl protease inhibitors; (ii) methods for modulating the processing of an amyloid precursor protein (APP); (iii) methods for modulating the processing of a tau protein (τ-protein); and (iv) methods for treating neurodegenerative diseases. For instance, in one embodiment, the present invention provides a method for modulating the processing of an amyloid precursor protein (APP), the method comprising contacting a composition containing the APP with an aspartyl protease inhibitor having the formula:



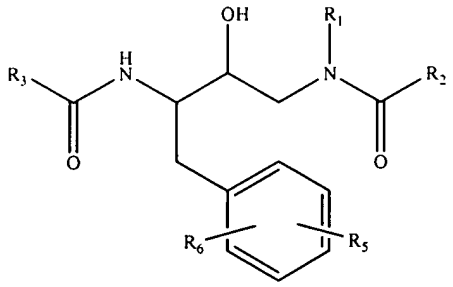
wherein:

R_1, R_2 and R_3 are members independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, aryloxyalkyl, substituted aryloxyalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycles, substituted heterocycles, heterocyclicalkyl and substituted heterocyclicalkyl; and R_5 and R_6 are independently selected from the group consisting of hydrogen, halogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, aryloxyalkyl and substituted aryloxyalkyl; or R_5 and R_6 and the carbons to which they are bound join to form an optionally substituted carbocyclic or heterocyclic fused ring system having a total of 9- or 10-ring atoms within the fused ring system.

In the claims

Claims 1, 5, 19, 23, 36 and 43 have been amended as follows:

1. A method for modulating the processing of an amyloid precursor protein (APP), said method comprising contacting a composition containing said APP with an aspartyl protease inhibitor having the [general] formula:



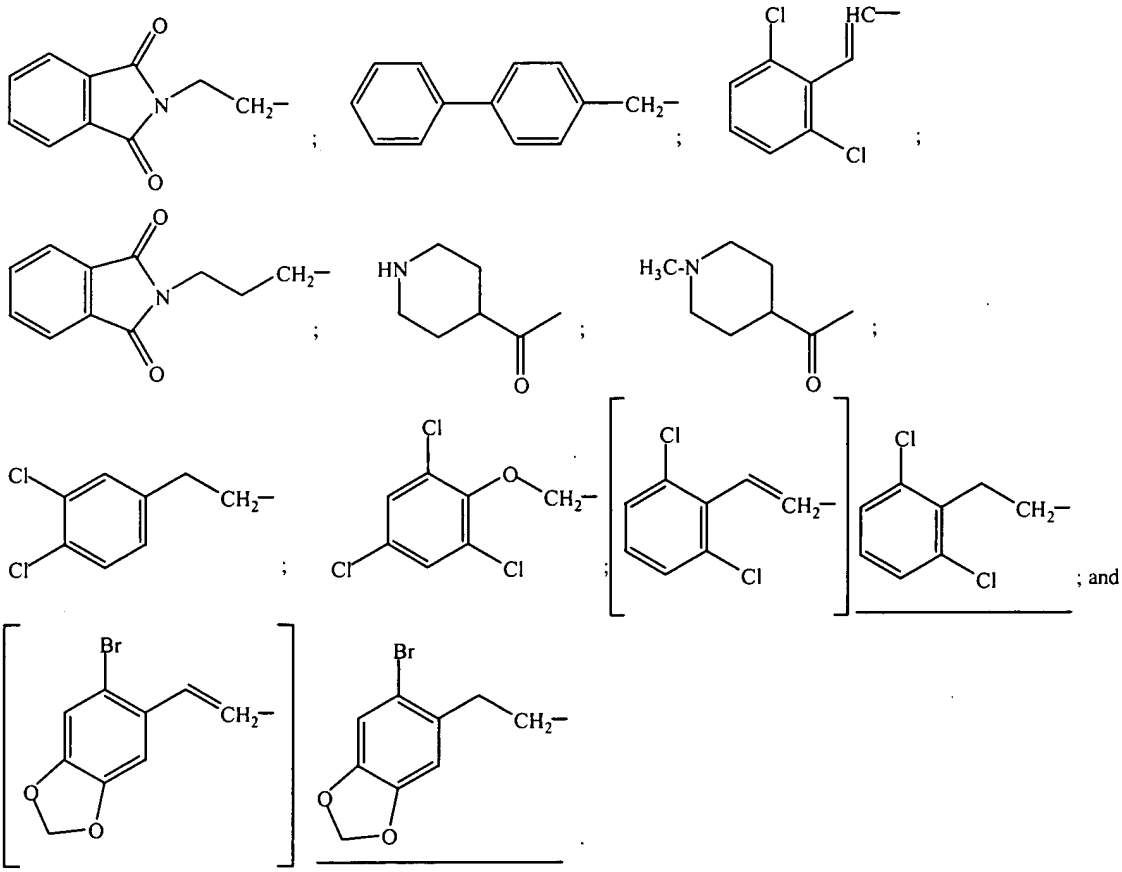
(I)

wherein:

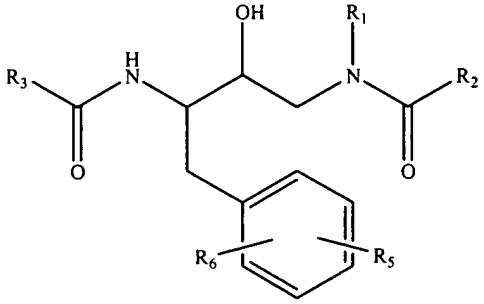
R_1, R_2 and R_3 are members independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, aryloxyalkyl, substituted aryloxyalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycles, substituted heterocycles, heterocyclicalkyl and substituted heterocyclicalkyl; and

R_5 and R_6 are independently selected from the group consisting of hydrogen, halogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, aryloxyalkyl and substituted aryloxyalkyl; or R_5 and R_6 and the carbons to which they are bound join to form an optionally substituted carbocyclic or heterocyclic fused ring system having a total of 9- or 10-ring atoms within said fused ring system.

5. The method according to claim 4, wherein R_2 is a member selected from the group consisting of:



19. A method for modulating the processing of a tau-protein (τ-protein), said method comprising contacting a composition containing said τ-protein with an aspartyl protease inhibitor having the [general] formula:



(I)

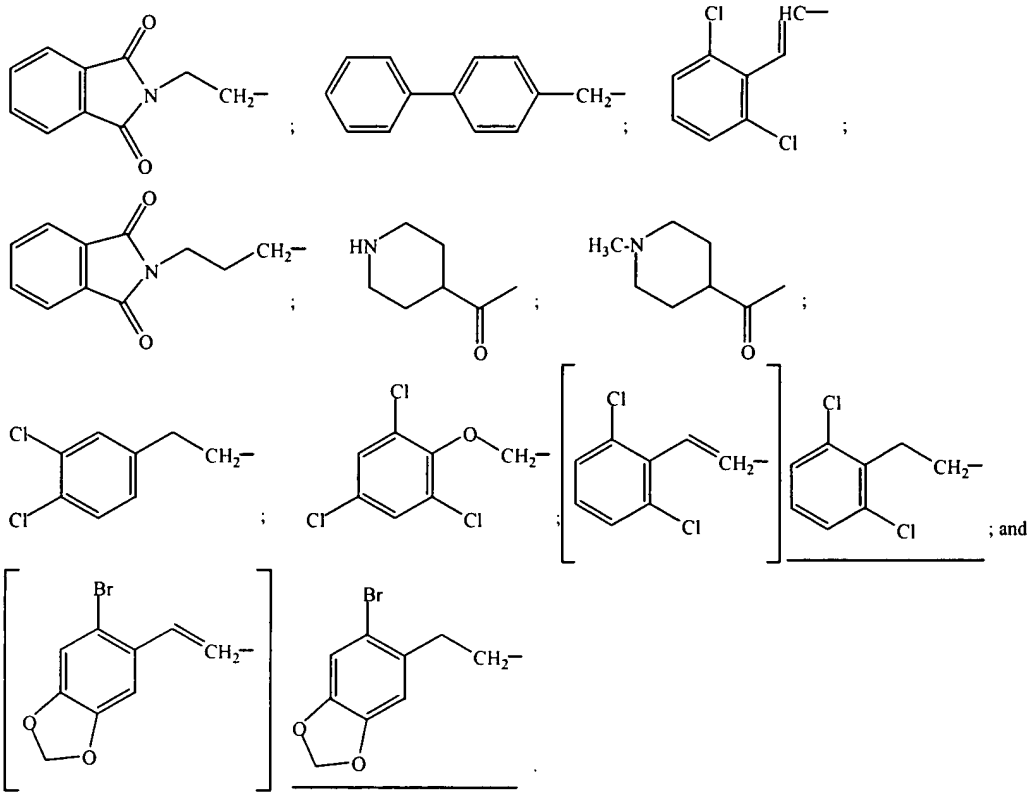
wherein:

R_1, R_2 and R_3 are members independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, aryloxyalkyl, substituted aryloxyalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycles,

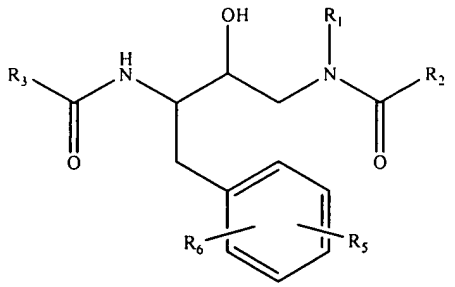
substituted heterocycles, heterocyclicalkyl and substituted heterocyclicalkyl; and

R_5 and R_6 are independently selected from the group consisting of hydrogen, halogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, aryloxyalkyl and substituted aryloxyalkyl; or R_5 and R_6 and the carbons to which they are bound join to form an optionally substituted carbocyclic or heterocyclic fused ring system having a total of 9- or 10-ring atoms within said fused ring system.

23. The method according to claim 22, wherein R_2 is a member selected from the group consisting of:



36. A method for treating a neurodegenerative disorder, said method comprising: administering to a mammal a therapeutically effective amount of an aspartyl protease inhibitor having the [general] formula:



(I)

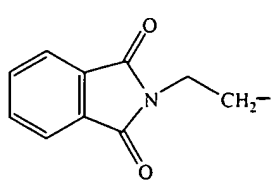
wherein:

R_1, R_2 and R_3 are members independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, aryloxyalkyl, substituted aryloxyalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycles, substituted heterocycles, heterocyclicalkyl and substituted heterocyclicalkyl; and

R_5 and R_6 are independently selected from the group consisting of hydrogen, halogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, aryloxyalkyl and substituted aryloxyalkyl; or R_5 and R_6 and the carbons to which they are bound join to form an optionally substituted carbocyclic or heterocyclic fused ring system having a total of 9- or 10-ring atoms within said fused ring system; and

a pharmaceutically acceptable carrier.

43. The method according to claim 42, wherein R_2 is a member selected from the group consisting of: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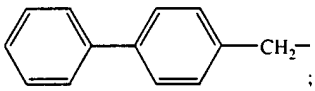
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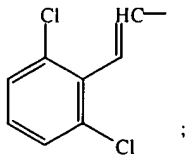
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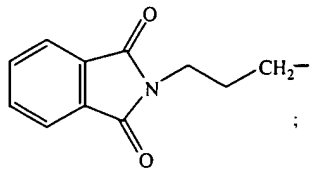
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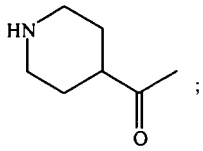
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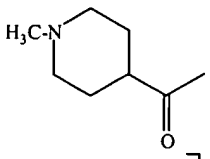
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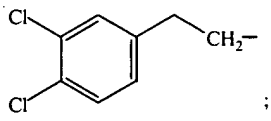
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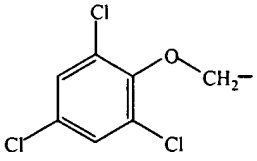
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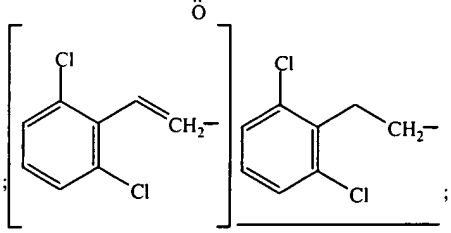
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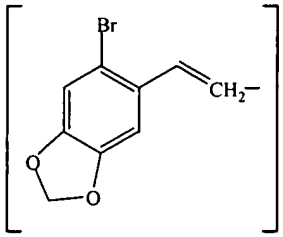
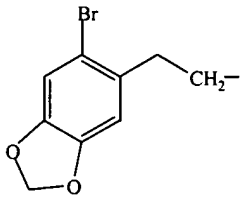
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